JAB 287

IN THE UNITED STATES
PATENT AND TRADEMARK OFFICE

Inventors : Jan Heeres and Leo J. J. Backx

U.S. Patent No.: 4,267,179

Issued : May 12, 1981

For : HETEROCYCLIC DERIVATIVES OF (4-PHENYLPIPERAZIN-1-YL-ARYLOXYMETHYL-1,3-DIOXOLAN-2-YL)METHYL-1*H*-IMIDAZOLES AND 1*H*-1,2,4-TRIAZOLES

Hon. Commissioner of Patents and Trademarks
Box Patent EXT
Washington, D.C. 20231

APPLICATION FOR EXTENSION OF
PATENT TERM UNDER 35 U.S.C. 156

Dear Sir:

Applicant Janssen Pharmaceutica N.V., a Belgian business corporation, represents that it is the assignee of the entire interest in and to Letters Patent of the United States No. 4,267,179 granted to Jan Heeres and Leo J. J. Backx on May 12, 1981, by virtue of an assignment to Janssen Pharmaceutica N.V. recorded in the United States Patent and Trademark Office on December 22, 1980, at reel 3815, frame 066.

Applicant hereby submits this Application for Extension of Patent Term under 35 U.S.C. 156 and provides the following information according to the relevant regulations set out at 37 C.F.R. 1.710 *et seq*. The numbering of the following paragraphs corresponds to the numbering of the requirements for an application set forth in 37 C.F.R. 1.740.

The active ingredient covered by U.S. Patent No. 4,267,179 is itraconazole. Itraconazole is approved as safe and effective for oral administration to humans as an anti-fungal drug in the treatment of blastomycosis, pulmonary and extrapulmonary, and histoplasmosis, including chronic cavitary pulmonary disease and disseminated, non-meningeal histoplasmosis. The complete identification of itraconazole is the following:

Itraconazole is a 1:1:1:1 racemic mixture of four diastereomers (two enantiomeric pairs), each possessing three chiral centers which are indicated by asterisks in the chemical formula presented below.

Chemical Name:

(±)-1-[(*R**)-*sec*-butyl]-4-[*p*-[4-[*p*-[[(2*R**,4*S**)-2-(2,4-dichlorophenyl)-2-(1*H*-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]-methoxy]phenyl]-1-piperazinyl]phenyl]-Δ^2-1,2,4-triazolin-5-one mixture with (±)-1-[(*R**)-*sec*-butyl]-4-[*p*-[4-[*p*-[[(2*S**,4*R**)-2-(2,4-dichlorophenyl)-2-(1*H*-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-Δ^2-1,2,4-triazolin-5-one.

Alternative names for itraconazole are the following:

(±)-*cis*-4-[4-[4-[4-[[2-(2,4-dichlorophenyl)-2-(1*H*-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]-

phenyl]-2,4-dihydro-2-(1-methylpropyl)-3*H*-1,2,4-triazol-3-one; or

(±)-1-[(*RS*)-*sec*-butyl]-4-[*p*-[4-[*p*-[[(2*R*,4*S*)-2-(2,4-dichlorophenyl)-2-(1*H*-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]-methoxy]phenyl]-1-piperazinyl]phenyl]-Δ^2-1,2,4-triazolin-5-one.

Generic Name:

itraconazole

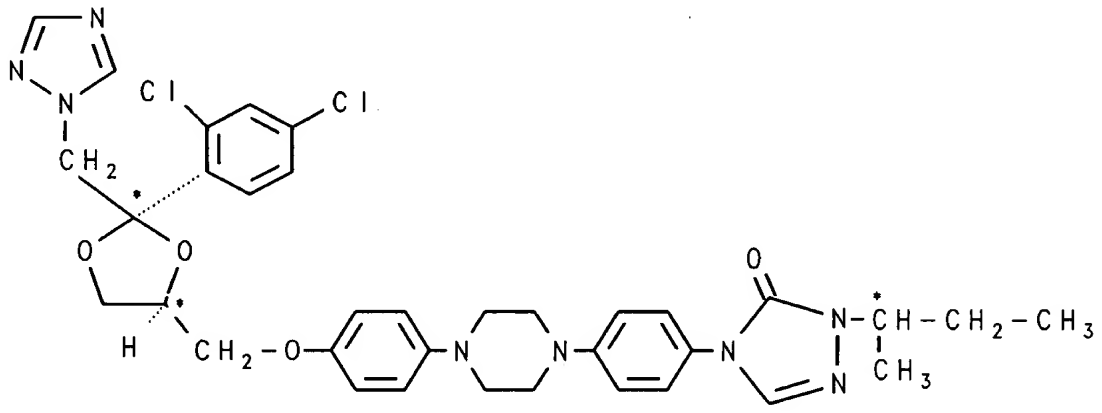
Manufacturer's Research Number:

R 51,211

Manufacturer's Registered Trade Name:

Sporanox

Molecular Structure:



Characteristics:

- melting point 166.2°C (crystallized from toluene)
- molecular formula $C_{35}H_{38}Cl_2N_8O_4$

(2)

The approved product was subject to regulatory review under the Federal Food, Drug and Cosmetic Act, Section 505 (21 U.S.C. 355).

(3)

The approved product received permission for commercial marketing or use under Section 505 of the Federal Food Drug and Cosmetic Act (21 U.S.C. 355) on the following date:

September 11, 1992.

(4)

The approved product is a human drug product containing itraconazole as the active ingredient. See paragraph (1) above for a more complete description of itraconazole. Itraconazole has not been previously approved for commercial marketing or use as a human drug product under Section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355).

(5)

This application for extension of patent term under 35 U.S.C. 156 is being submitted within the sixty (60) day period permitted for submission pursuant to 37 C.F.R. 1.720(f). The last day on which this application could be submitted is November 10, 1992.

(6)

The complete identification of the patent for which this extension is being sought is as follows:

Inventors: Jan Heeres and Leo J. J. Backx
Patent Number: 4,267,179
Date of Issue: May 12, 1981
Date of Expiration: May 12, 1998

(7)

A copy of the patent for which an extension is being sought is appended hereto as Exhibit A. (Four extra copies of the patent are included herewith.)

(8)

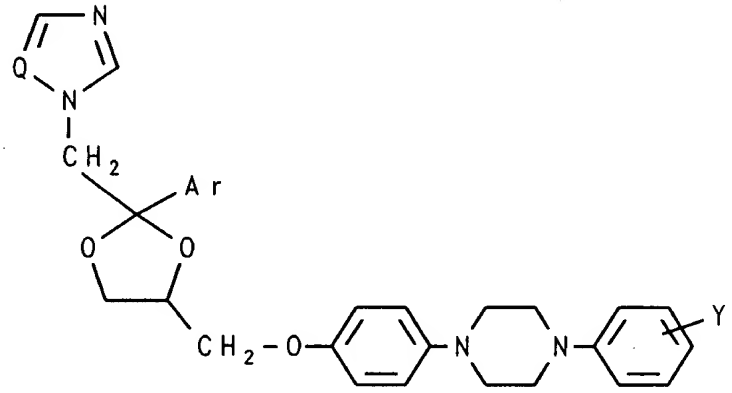
The records of the undersigned do not indicate that any disclaimer, certificate of correction, receipt of maintenance fee payment, or reexamination certificate were issued in the patent identified in paragraph (6). A Request for Certificate of Correction

has been filed (dated September 24, 1992) in order to correct an error appearing in a formula in Claims 1 and 7. A copy of the Request for Certificate of Correction is included herewith as Exhibit B.

(9)

United States Patent Number 4,267,179 claims the approved product both as a chemical compound and as a composition for combatting the growth of fungi and bacterium comprising an inert carrier and as the active ingredient the approved product. Claims 1 and 7 are relevant:

1. A chemical compound selected from the group consisting of an azole derivative having the formula:



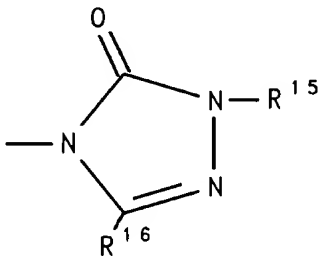
and the pharmaceutically acceptable acid addition salts and stereochemically isomeric forms thereof, wherein:

Q is a member selected from the group consisting of CH or N;

Ar is a member selected from the group consisting of phenyl, thienyl, halothienyl and substituted phenyl, said substituted phenyl having from 1 to 3 substituents each independently selected from the

group consisting of halo, lower alkyl, lower alkyloxy and trifluoromethyl; and

the radical Y is a 2,3-dihydro-4*H*-1,2,4-triazol-4-yl radical of the formula



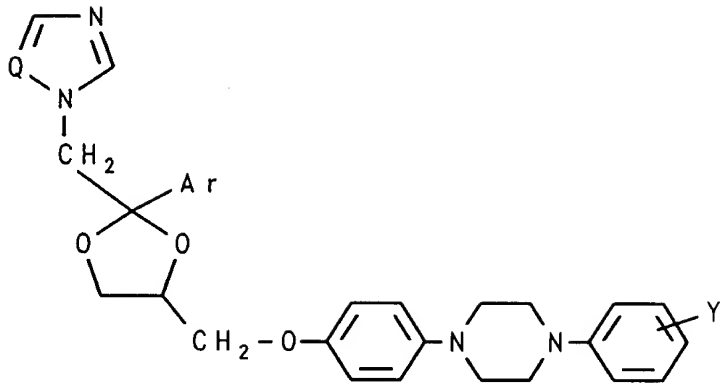
(f)

wherein R^{15} is selected from the group consisting of lower alkyl and aryl lower alkyl and R^{16} is selected from the group consisting of hydrogen, lower alkyl, and aryl lower alkyl;

wherein said aryl as used in the foregoing definition is selected from the group consisting of phenyl and substituted phenyl, said substituted phenyl having from 1 to 3 substituents each independently selected from the group consisting of halo, lower alkyl, lower alkyloxy and trifluoromethyl.

[Note - corrected Formula (f) is shown; reference is made to the Request for Certificate of Correction mentioned above in Paragraph (8).]

7. A composition for combatting the growth of a microorganism selected from the group consisting of fungus and bacterium comprising an inert carrier material and as an active ingredient an effective antifungal or antibacterial amount of a compound selected from the group consisting of an azole derivative having the formula:

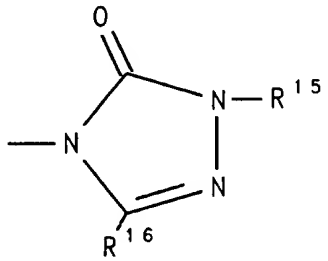


and the pharmaceutically acceptable acid addition salts and stereochemically isomeric forms thereof, wherein:

Q is a member selected from the group consisting of CH or N;

Ar is a member selected from the group consisting of phenyl, thienyl, halothienyl and substituted phenyl, said substituted phenyl having from 1 to 3 substituents each independently selected from the group consisting of halo, lower alkyl, lower alkyloxy and trifluoromethyl; and

the radical Y is a 2,3-dihydro-4*H*-1,2,4-triazol-4-yl radical of the formula



(f)

wherein R^{15} is selected from the group consisting of lower alkyl and aryl lower alkyl and R^{16} is selected from the group consisting of hydrogen, lower alkyl, and aryl lower alkyl;

wherein said aryl as used in the foregoing definition is selected from the group consisting of phenyl and substituted phenyl, said substituted phenyl having from 1 to 3 substituents each independently selected from the group consisting of halo, lower alkyl, lower alkyloxy and trifluoromethyl.

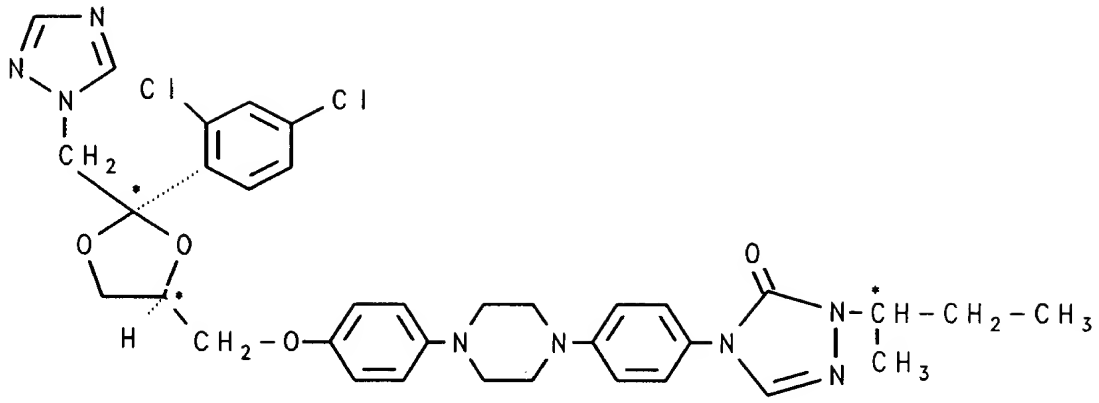
[Note - corrected Formula (f) is shown; reference is made to the Request for Certificate of Correction mentioned above in Paragraph (8).]

The following is a demonstration of the manner in which each of Claims 1 and 7 of the patent reads on the approved product:

The approved product is itraconazole, an anti-fungal compound identified chemically as:

(±)-1-[(*R**)-*sec*-butyl]-4-[*p*-[4-[*p*-[[(2*R**,4*S**)-2-(2,4-dichlorophenyl)-2-(1*H*-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]-methoxy]phenyl]-1-piperazinyl]phenyl]-Δ^2-1,2,4-triazolin-5-one mixture with (±)-1-[(*R**)-*sec*-butyl]-4-[*p*-[4-[*p*-[[(2*S**,4*R**)-2-(2,4-dichlorophenyl)-2-(1*H*-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-Δ^2-1,2,4-triazolin-5-one.

Itraconazole has the following structural formula:



In the general formula shown in each claim, when the following are selected, itraconazole is obtained:

Q = N;

Ar = substituted phenyl having two halo substituents wherein halo is chloro (see Col. 3, line 43); and

Y = formula (f), wherein in formula (f):

R^{15} = lower alkyl wherein lower alkyl is 1-methylpropyl (see Col. 3, lines 44-48, especially lines 47-48); and

R^{16} = hydrogen.

Please note further that both claims recite that "stereochemically isomeric forms" of the compound represented by the structural formula are included within the scope of the claimed invention. Itraconazole consists of the 1:1:1:1 mixture of all four possible stereochemically isomeric forms in which the (1*H*-1,2,4-triazole-1-ylmethyl) moiety and the substituted phenoxy moiety are located on the same side of the plane defined by the 1,3-dioxolane ring.

(10)

The relevant dates and information pursuant to 35 U.S.C. 156(g) to enable the Secretary of Health and Human Services to determine the applicable regulatory review periods are as follows:

(a) The Investigational New Drug (IND) application [i.e., the application for exemption under subsection (i) of section 505 of the Federal Food, Drug, and Cosmetic act (21 U.S.C. 355(i)] under which the clinical studies were performed which were referenced in the New Drug Application (NDA) referred to in sub-paragraph (10)(b) below was filed on June 1, 1984, by Janssen Research Foundation. The application was effective as of June 7, 1984, and it was assigned IND #24,313.

(b) The New Drug Application (NDA) [i.e., the application for approval under subsection (b) of section 505 of the Federal Food, Drug, and Cosmetic act (21 U.S.C. 355(b)] for itraconazole was submitted on May 30, 1990, by Janssen Research Foundation, and was assigned NDA #20-083.

(c) The date on which NDA #20,083 was approved was September 11, 1992.

(11)

(a) A brief description of the significant activities and dates applicable to such activities undertaken by or on behalf of the marketing applicant during the applicable regulatory review with respect to the approved product is set forth below in subparagraphs (11)(b) and (11)(c). In this regard, it should be noted that the Applicant herein is Janssen Pharmaceutica N.V., a corporation of Belgium and a wholly-owned subsidiary of Johnson & Johnson, a corporation of New Jersey, U.S.A. While U.S. Patent No. 4,267,179 has been and is now owned by Janssen Pharmaceutica N.V., the IND and NDA submissions and activities described herein were undertaken by Janssen Research Foundation, a Delaware corporation, which is a wholly owned subsidiary of Johnson & Johnson. (The Janssen Research Foundation will occasionally be referred to hereinafter as "JRF".) All IND and NDA activities undertaken as described below in subparagraphs (11)(b) and (11)(c) were carried out with the full and complete permission of Janssen Pharmaceutica N.V. and Johnson & Johnson.

(b) Relevant Activities Under IND 24,313

June 1, 1984 - IND submitted to Federal Food and Drug Administration ("FDA") by JRF.

June 7, 1984 - Effective date of IND 24,313.

August 24, 1984 - Date first study submitted to FDA.

November 15, 1988 - Pre-NDA meeting with FDA (copy of the minutes of that meeting attached hereto as Exhibit C). JRF requested by FDA to prepare individual patient summaries written by the investigators for comparison with patient case record forms, prior to submission of NDA.

January 27 and February 7, 1989 - Telephone conversations with FDA. FDA requested that the format of the case record forms be changed to the format used by the NIH, and to have all X-rays reviewed retrospectively on a blinded basis by an uninvolved third party. Copies of memos of telephone conversations included herewith as Exhibits D and E.

March 1, 1989 - Telephone conversation with FDA. Patient summaries, bioavailability, and Phase IV studies were discussed. Memo of conversation included herewith as Exhibit F.

(c) Relevant Activities Under NDA 20-083

1.	Date submitted to FDA by JRF	May 30, 1990
2.	Date received	May 31, 1990
3.	Biopharmaceutics Comments	June 12, 1990
	Requests for assay validation data and statistical analysis for various studies	
	Responses	August 17, 1990 August 30, 1990 September 28, 1990 October 29, 1990 November 8, 1990
4.	Submission of overall summary of NDA	July 33, 1990
5.	Meeting with FDA	July 27, 1990

	Requests for information on prior therapy, relapse rates, efficacy of ketoconazole and amphotericin B in histoplasmosis and blastomycosis and separate database for AIDS patients	
	Responses	August 28, 1990 September 12, 1990
6.	NDA filed	July 30, 1990
7.	Chemistry comments	September 4, 1990
	Comments related to dissolution	
	Responses	November 20, 1990 February 7, 1991 March 8, 1991
8.	Chemistry comments	September 11, 1990
	Comments related to stereochemistry	
	Responses	October 24, 1990 November 1, 1990
9.	Amendment adding Gurabo (Janssen manufacturing plant in Puerto Rico) as manufacturer	October 4, 1990
10.	Pharmacology comments	October 16, 1990
	Responses	November 7, 1990 November 15, 1990 November 29, 1990
11.	Receipt of FDA's policy statement on methylene chloride content	October 30, 1990
	Responses	November 20, 1990 January 8, 1991
12.	Submission of the environmental assessment	November 16, 1990
13.	Telephone conversation with FDA - NDA considered to be non-approvable	December 6, 1990
14.	Chemistry meeting with FDA	February 19, 1991
15.	Chemistry Commitments	March 6, 1991 March 21, 1991
16.	Meeting with FDA Status of NDA - Unapprovable mainly owing to high methylene chloride content	March 28, 1991

17.	Withdrawal of NDA	April 26, 1991
18.	Resubmission of NDA; new formulation with reduced methylene chloride content	October 10, 1991
19.	Teleconference with FDA FDA requests statement about lung carcinoma be added to labeling; chemist requests revision in dissolution method	October 18, 1991
	Responses	December 17, 1991 December 20, 1991
20.	Resubmitted NDA filed	November 7, 1991
21.	Teleconference with FDA Biopharmaceutical reviewer states bioequivalence study is needed to show old and new formulations are equivalent	November 15, 1991
	Response (report of pilot study)	November 18, 1991
22.	Teleconference with FDA Biopharmaceutical reviewer requests side-by-side dissolution profiles for the lots used in the biostudy	November 25, 1991
	Response	December 19, 1991
23.	Labeling negotiations - FDA rewrites package insert	January 24, 1992 January 27, 1992 January 30, 1992 February 6, 1992 February 21, 1992 April 14, 1992
	Responses	February 4, 1992 March 6, 1992 May 1, 1992
24.	Submission of chemistry amendments	February 4, 1992 March 27, 1992 May 8, 1992 June 12, 1992 June 17, 1992
25.	Pre-approval inspection	March 1992
	Response	May 8, 1992
26.	Labeling teleconferences	May 1, 1992 May 12, 1992

27.	Submission of Phase IV commitments	May 29, 1992
28.	Submission of final version of package insert	June 2, 1992
29.	Teleconference with FDA regarding labeling - FDA requests black box warning for terfenadine interaction	July 1, 1992 July 2, 1992
30.	Package insert resubmitted Requested revisions incorporated	July 7, 1992
31.	Final version of package insert submitted Requested revisions incorporated	July 15, 1992
32.	Teleconference with FDA - office level comments on package insert	September 1, 1992 September 4, 1992 September 10, 1992 September 11, 1992
33.	Final version of package insert submitted Requested revisions incorporated	September 11, 1992
34.	NDA Approval	September 11, 1992

Applicant is of the opinion that U.S. Patent No. 4,267,179 is eligible for extension under 35 U.S.C. 156 because it satisfies all of the requirements for such extension, as follows:

i) 35 U.S.C. §156(a):

U.S. Patent No. 4,267,179 claims a product (new chemical entity).

ii) 35 U.S.C. §156(a)(1):

The term of U.S. Patent No. 4,267,179 has not expired before submission of the present application.

iii) 35 U.S.C. §156(a)(2):

The term of U.S. Patent No. 4,267,179 has never been extended.

iv) 35 U.S.C. §156(a)(3):

The Application for Extension is submitted by the owner of record through its agent in accordance with the requirements of 35 U.S.C. §156(d).

v) 35 U.S.C. §156(a)(4):

The approved product has been subject to a regulatory review period before its commercial marketing or use.

vi) 35 U.S.C. §156(a)(5)(A):

The permission for the commercial marketing or use of the product after such regulatory review period is the first permitted commercial marketing or use of the product under the provisions of the Federal Food, Drug and Cosmetic Act (21 U.S.C. §355) under which such regulatory review period occurred.

The length of extension claimed in the present application is four (4) years, one (1) month and eighteen (18) days from May 12, 1998. The requested four (4) year, one (1) month and eighteen (18) day extension is the duration provided for by 35 U.S.C. §156(c)(2). The requested extension does not exceed the fourteen year maximum from the date of approval imposed by 35 U.S.C. §156(c)(3). This extension is supported by the regulatory review period for the approved product, which was eight (8) years, three (3) months and four (4) days, beginning on June 7, 1984, the effective date of IND 24,313. and ending on September 11, 1992, the date on which the approved product received permission for commercial marketing under 21 U.S.C. 255..

(13)

The Applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extension sought in the present application for extension.

(14)

Accompanying this application is a transmittal letter which requests that the required fee for the present application for extension to be charged to Deposit Account Number 10-750/JAB 287/CJM.

(15)

The name, address, and telephone number of the person to whom inquiries and correspondence relating to the present application for patent term extension are to be directed is as follows:

Address:	Audley A. Ciamporcero Johnson & Johnson One Johnson & Johnson Plaza New Brunswick, New Jersey 08933-7003
Telephone Calls:	Charles J. Metz (908) 524-2814

(16)

A duplicate of this application is enclosed. The required certification is appended hereto as Exhibit G.

(17)

The Declaration required by 37 C.F.R. 1.740(b) is attached hereto as Exhibit H.

Respectfully submitted,

Charles J. Metz
Registration No. 20,359
Attorney for Applicant

Johnson & Johnson
One Johnson & Johnson Plaza
New Brunswick, New Jersey 08933-7003
(908) 524-2814

October 29, 1992

EXHIBIT A

United States Patent [19]

Heeres et al.

[11] **4,267,179**

[45] **May 12, 1981**

[54] **HETEROCYCLIC DERIVATIVES OF (4-PHENYLPIPERAZIN-1-YL-ARYLOXYMETHYL-1,3-DIOXOLAN-2-YL)METHYL-1H-IMIDAZOLES AND 1H-1,2,4-TRIAZOLES**

[75] Inventors: **Jan Heeres**, Vosselaar; **Leo J. J. Backx**, Arendonk, both of Belgium

[73] Assignee: **Janssen Pharmaceutica, N.V.**, Beerse, Belgium

[21] Appl. No.: **20,383**

[22] Filed: **Mar. 14, 1979**

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 919,333, Jun. 23, 1978, abandoned.

[51] **Int. Cl.**[3] **A61K 31/495**; C07D 405/14

[52] **U.S. Cl.** ..... **424/25 D**; 544/366; 544/370; 544/371; 544/372; 548/262; 548/341; 260/340.9 R

[58] **Field of Search** 544/366, 370, 371; 424/250

[56] **References Cited**

U.S. PATENT DOCUMENTS

3,936,470	2/1976	Heeres	424/273
4,144,346	3/1979	Heeres et al.	424/273

Primary Examiner—Donald G. Daus
Assistant Examiner—James H. Turnipseed
Attorney, Agent, or Firm—Geoffrey G. Dellenbaugh

[57] **ABSTRACT**

Novel heterocyclic derivatives of (4-phenylpiperazin-1-yl-aryloxymethyl-1,3-dioxolan-2-yl)methyl-1H-imidazoles and 1H-1,2,4-triazoles, useful as antifungal and antibacterial agents.

7 Claims, No Drawings

EXHIBIT B

Johnson & Johnson

OFFICE OF
GENERAL COUNSEL

ONE JOHNSON & JOHNSON PLAZA
NEW BRUNSWICK, N.J. 08933-7003

September 24, 1992

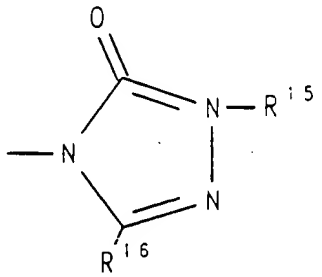
The Hon. Commissioner of
Patents & Trademarks
Washington, D.C. 20231

Re: U.S. Patent No. 4,267,179
Serial No. 20,383
Our File: JAB 287

Dear Sir:

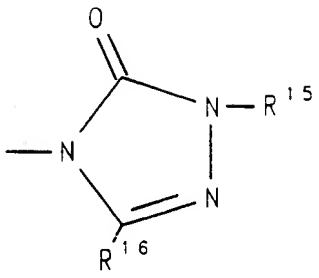
It is respectfully requested that a Certificate of Correction be issued to correct the errors as set forth in the attached form and in compliance with amended Rule 322.

The error resides in the formula identified as "(f)" in the specification at Col. 3, lines 1-8, and in Claims 1 and 7, appearing at Col. 40, lines 59-66, and at Col. 42, lines 29-35, respectively. As printed in the patent, the formula appears as follows:



(f)

The error in the formula resides in the double bond shown in the ring between the nitrogen atom bearing the variable R^{15} and the carbonyl group. This double bond should be shown as a single bond. Formula (f) as depicted in the application at page 4, lines 8-9, is shown correctly as follows:



(f)

In the Office Action of May 20, 1980, Examiner Tovar pointed out that the formula for the variable Y in Claim 15 (which was added by Amendment filed in the Patent and Trademark Office on September 13, 1979) was incorrect. In response to the Examiner's comments, by Amendment filed in the Patent and Trademark Office on August 25, 1980, Applicants corrected formula (f) in Claims 15 and 16 (which issued as Claims 1 and 7 in the patent), to read as shown immediately above.

In view of the foregoing, it is respectfully requested that a Certificate of Correction be issued to correct the formula identified as "(f)" in the specification at Col. 3, lines 1-8, and in Claims 1 and 7, appearing at Col. 40, lines 59-66, and at Col. 42, lines 29-35, respectively.

Very truly yours,

Charles J. Metz

Attorney for Assignee
Reg. No. 20,359

Attachment

One Johnson & Johnson Plaza
New Brunswick, NJ 08933-7003
(908) 524-2814

Staple Here Only I

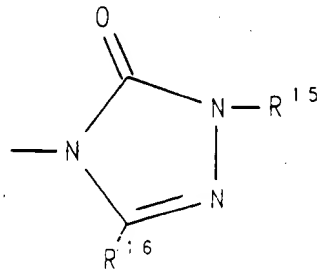
PRINTER'S TRIM LINE

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 4,267,179
DATED : May 12, 1981
INVENTOR(S) : Jan Heeres, Leo J. J. Backx

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Formula (f), appearing in the specification at Col. 3, lines 1-8, and in Claims 1 and 7, at Col. 40, lines 59-66, and at Col. 42, lines 29-35, respectively, at all three occurrences, should read as follows:



(f)

MAILING ADDRESS OF SENDER:
Charles J. Metz
1 Johnson & Johnson Plaza
New Brunswick, NJ 08933

PATENT NO. 4,267,179

No. of add'l. copies @ 30¢ per page

EXHIBIT C

JANSSEN
RESEARCH
FOUNDATION

TO: List

DATE: November 17, 1988

FROM: Ruth Wasserman

RE: Meeting With FDA on Itraconazole NDA

Minutes: Meeting with FDA on Itraconazole NDA

November 15, 1988

Attendees

FDA: Ellen Cooper, MD - Division Director
Paul Benninger, MD - Medical Supervisor
Ralph Lillie - Consumer Safety Officer
Janssen: Robert Legendre - Director, Infectious Diseases
Ruth Wasserman - Manager, Regulatory Affairs

This was the second one-on-one meeting designed to establish whether some of our clinical data, developed in non-controlled clinical trials, is persuasive enough for FDA to accept an NDA for one or more systemic fungal indications.

Dr. Benninger began by stating FDA's agenda:

1. What indications will be in the NDA?
2. What format will the NDA take? Specifically as it relates to historical controls.
3. Discussion on additional studies required (post-NDA, prior to approval).

INDICATIONS

R. Legendre presented a tabulation to make a case for aspergillosis, blastomycosis and coccidiodomycosis and pointed out that the response rate in the compassionate clearance studies was in patients who were failures (either lack of efficacy or intolerance) to other therapy.

Dr. Benninger pointed out that "failure on prior therapy" can lead to a "morass" in which eg. evaluating whether a prior efficacy failure is due to insufficient dose or insufficient time on therapy becomes quite difficult. He also said that aspergillosis and cocci were difficult to "score".

He then said that FDA would accept an NDA for histo and blasto and asked us whether we truly wanted to pursue paracocci. R. Wasserman indicated that paracocci was not a high priority in the U.S.

In doing the NDA, the compassionate clearance-and foreign patients will be considered supportive only.

R. Legendre gave Dr. Cooper a brief recap of why we had not conducted controlled studies. Dr. Cooper reviewed our blank CRF's for the studies and stated that it would be better if more objective clinical parameters, eg. pulmonary function testing, had been required.

Our CRF's and patient-by-patient summaries will probably need additional documentation, which is hopefully contained in each patient's medical records.

FDA will want the CRF's for all patients in the systemic studies for histo and blasto (about 110 patients). CRF's for all drop-outs due to adverse events in all U.S. itraconazole studies must be submitted. All other systemic patients, the U.S. short-term studies, the compassionate clearance program and the foreign experience must be properly evaluated and summarized for safety purposes.

Format-Historical Controls

Since the control to be used for these studies is meant to satisfy FDA's statutory requirements, FDA emphasized that a well organized discussion of historical data describing the natural progress of blasto and histo is critical to the success of our NDA. It would be best to present the above in the same terms that our efficacy data will be presented. Dr. Benninger did point out that since our protocol and CRF's are generic for systemic mycoses rather than specific for each mycosis, this will tend to make our data "highly variable". Our CRF's may make it difficult to define an "end point" - what is the duration of therapy, what is the relapse rate, what is the proper dose? How many patients were continued on therapy after they were "cured"?

Additional Studies

An active-controlled study (vs. ketoconazole) for both histo and blasto will need to be initiated in the period between NDA submission and approval, i.e. 1990. FDA suggested use of a double-dummy design. However, Dr. Cooper said they would consider other methods of blinding, such as randomization by a third party, e.g. pharmacy. This may be used to prevent patients from having to take 6 tablets or capsules at one time. The study need only show equivalence. Full details will be worked out with FDA later in order, per Dr. Benninger, that our energies be devoted towards the rapid development of the NDA!

These studies must be started but not completed prior to NDA approval.

FDA also requested that pharmacokinetics in patients 6-12 years and in patients 2-6 years be investigated. We mentioned that this could be difficult because of the small number of patients at different sites and Human Research Committee approvals.

Dr. Benninger mentioned the report by Graybill of a high proportion of increased blood pressure, decreased potassium and edema in a study he conducted.

Next Meeting

Janssen will develop our proposed data presentation formats for FDA review.

RW:io

List

J. Butler
C. Barranco
G. Cauwenbergh
J. Carter
J. Demko-Macre
S. Freilich
A. Hsuan
D. Jackson
I. Katz
R. Legendre
D. Mallegol
L. Morra
R. Munies
D. Olsen
D. Parks
J. Ray
L. Roemer
V. Schuermans
L. Schwalbe
D. Shand
L. Suttner

EXHIBIT D

To: Distribution
From: C. Barranco
Re: Telephone conversation with Paul Benninger and Ralph Lilly of FDA on 1/27/89
Date: 1.27/89

The reason this contact was made was to find out if the sample narrative summaries we had sent to FDA in October were of an acceptable nature to Dr. Benninger in terms of content, style, format, etc. To my surprise, he began by sharing comments of his review of the NIH 6-A case record forms. These suggestions will apply to the new CRF supplement we recently mailed to our Janssen investigators, also.

On the Pre-Treatment form, page 2, item # 7, which is a check-off list of the baseline signs and symptoms, Dr. Benneinger would like to see a column added for "Duration"; that is, he wants to know how long a patient had fever, hemoptysis, joint pain, and so on , before starting itraconazole.

Regarding Item # 9 on that same page, he wants us to make provision to have all the chest x-rays reviewed retrospectively on a blinded basis by an uninvolved third party.

Regarding the Final Treatment Form, Item #6, he wants to know the outcome for all patients treated with itraconazole, not just those treated for 3 months or more. (This item has the investigator check "responder" or "non-responder" if the patient received 3 months or more of itra.) He stated that if the patient dropped due to an adverse reaction at Day 2, that this could be treated separately; that if a patient disappeared after 30 days, this too could be dealt with separately. But all cases have to be accounted for and evaluated.

Then we talked about the narrative summaries. He said that the ones I had written were very good and that they could be used as model for Dr. Dismukes, particularly the comments section. However, he suggested only one case per page. He stressed that whoever goes through the charts for Dr. Dismukes must "pull out as much (data) as possible."

We discussed that Dr. Dismukes would write 4-5 case summaries initially and that we would send them to him (Benninger) for review before having Dismukes go forward with writing the rest.

For each patient in the NDA, Benninger stated that he would like to see three items put together per patient:

1) the case record form (presumably with the supplementary information previously asked for)
2) The results of the blinded review of the x-rays.
3) The narrative summary

The next thing Dr. Benninger brought up was the natural history report that Dr. Bennett had written and had shown him at the MSG meeting this month. He stated that it was exactly the kind of information needed, that it was good information

and well-described. However, he said that the next step is to "pull the historical cases apart and treat them like case record forms." What are the details of the clinical courses of these patients being described-- duration of fever, hemoptysis, pain etc.

Then, he began to talk about paracoccidioidomycosis. He said he was optimistic about it and that we should include it in the report on the natural course of diseases. He stated that, even though we don't see much of it here, it was probably something we should include in the NDA!

Suggested Actions to be Taken:

1. Revise the CRF supplement to the Janssen CRF ASAP to include the "duration" column next to baseline s&s.
2. Ask Dismukes to get the NIH investigators to add the duration of the baseline signs and symptoms to the case record forms (originals or copies?)
3. Send model narrative summaries to Dismukes and ask him to write the first 5 summaries
4. Ask Dismukes to get the NIH investigators to evaluate patients treated less than 3 months, if necessary.(Debbie and Michelle)
5. Formulate a plan to have the chest x-rays read at the local institutions by a blinded, third party radiologist. Cost? Form for the data?
6. Contact Bennett about: 1)more detail to his historical report and (2) adding paracocci to it. (Bob?)
7. Discuss on 1/31/89 whether to pursue the paracocci claim.

Distribution:

Bob Legendre
Ruth Wasserman
Bob Munies
David Jackson

EXHIBIT E

JANSSEN
RESEARCH
FOUNDATION

TO: List

DATE: February 7, 1989

FROM: Ruth Wasserman

RE: Telephone Conference with Paul Benninger FDA, on Itraconazole - 2/3/89

C. Barranco, R. Legendre and I spoke with Dr. Benninger regarding his 1/27/89 additional requests for documentation for the itraconazole NDA which he had discussed with C. Barranco.

1. Need to have x-rays read by a blinded radiologist

   If the original x-rays were read by a radiologist who did not know the patient was participating in a study, then a copy of the radiologist's reports should be obtained and included with that patient's CRF.

   If the original evaluations were not as described above, they all should be re-read blinded at the site. They do not have to be read by one central radiologist.

2. Duration of each sign/symptom at entry

   Dr. Benninger thinks that this information could be useful to predict time to response. He envisions that a linear regression analysis would determine if a correlation exists.

   He told us to "do your best" to obtain this retrospective information, and went on to explain that he is "not inflexible".

3. Sample patient summaries

   During our discussions, we became aware that it was not just a patient summary, but a whole packet that should be submitted

   - CRF with sign/symptom durations
   - X-ray evaluations
   - Summary

   It was agreed that three blasto and three histo examples would be submitted as soon as possible.

4. Paracocci

It was agreed to hold off on that for now.

RW:io

List

C. Barranco
R. Beckman
J. Butler
J. Esola-Macre
J. Guarnieri
D. Jackson
I. Katz
R. Legendre
R. Munies
L. Roemer
L. Schwalbe
D. Shand
L. Suttner

EXHIBIT F

TO: Robert Legendre

FROM: Ruth Wasserman

DATE: March 1, 1989

RE: Itraconazole - Phone Call from FDA 2/28/89

Dr. Paul Benninger and Ralph Lillie called to go over several items because they are committed to getting this NDA expedited.

1. Patient Summaries

   He asked about the status of the 3 blasto and 3 histo summaries. I explained to him briefly how our review of the summaries/CRFs vs. the source documents had raised doubts in our minds about the diagnoses of some of Dr. Dismukes' patients. I went on to explain that we planned to have a doctor and monitor go to Alabama next week to resolve this issue. Dr. Benninger asked us to get this resolved and to submit the summaries "with all deliberate speed".

2. He asked me to keep Mr. Lillie up-to-date on NDA matters via telephone every week or two.

3. He asked us to consider expanding the NDA to include paracocci if at all possible.

4. Bioavailability

   Dr. Benninger had asked FDA's Pharmacokinetics Branch to review the 10-subject bioequivalence report that compared the PEG capsule to the pellet capsule. This report, N-54007, CRR 51.211/30, had been submitted to the IND in July, 1987 when the clinical supplies were changed.

   The study - on its own - is deemed inadequate because insufficient subjects are included and because assay validation was not present.

   I explained that the NDA would have two 24-subject studies (PEG vs. reference solution, and pellet vs. reference solution) as well as assay validation. These reports had not been submitted to the IND. I offered to send them down promptly and Dr. Benninger was relieved that these reports were available. (I will hand deliver the packet next week before we see Dr. Huene.)

5. Phase IV Studies

Dr. Benninger asked that we develop an outline of the studies we will do after the NDA is submitted/approved. Once this outline is discussed with FDA, we and FDA can find out who will do them.

The outline should indicate the studies planned for spectrum of disease, other indications, pediatrics, other formulations (i.v./solution). Examples (not suggestions) given: spectrum of disease: initial treatment vs. amphotericin failures; other indications: cocci, aspergillosis; children: prophylaxis during chemotherapy.

RW:io

c: C. Barranco
J. Butler
G. Cauwenbergh
J. Esola-Macre
A. Hsuan
D. Jackson
R. Munies
L. Roemer
D. Shand
L. Schwalbe
L. Suttner

JAB 287

EXHIBIT G

IN THE UNITED STATES
PATENT AND TRADEMARK OFFICE

Inventors : Jan Heeres and Leo J. J. Backx

U.S. Patent No.: 4,267,179

Issued : May 12, 1981

For : HETEROCYCLIC DERIVATIVES OF (4-PHENYLPIPERAZIN-1-YL-ARYLOXYMETHYL-1,3-DIOXOLAN-2-YL)METHYL-1*H*-IMIDAZOLES AND 1*H*-1,2,4-TRIAZOLES

Hon. Commissioner of Patents and Trademarks
Box Patent EXT
Washington, D.C. 20231

CERTIFICATION

I hereby certify that this Application for Extension of Patent Term Under 35 U.S.C. §156, as well as all Exhibits A through H thereto, is being submitted in duplicate to the Commissioner of Patents and Trademarks, Box Patent EXT, Washington, D.C. 20231

Date: October 29, 1992

Charles J. Metz
Registration No. 20,359
Attorney for Applicants

Johnson & Johnson
One Johnson & Johnson Plaza
New Brunswick, NJ 08933-7003

(908) 524-2814

STATE OF NEW JERSEY)
)
) ss.
)
COUNTY OF MIDDLESEX)

BE IT REMEMBERED, that on this 29th day of October, 1992, before me, a Notary Public, personally appeared Charles J. Metz, who I am satisfied is the person named in and who executed the foregoing instrument in my presence, and I having first made known to him the contents thereof, he did acknowledge that he signed, sealed, and delivered the same as his voluntary act and deed for the uses and purposes therein expressed.

Joan Weiss
Notary Public

JOAN WEISS
Notary Public of New Jersey
My Commission Expires Sept. 11, 1995

EXHIBIT H

IN THE UNITED STATES
PATENT AND TRADEMARK OFFICE

Inventors	:	Jan Heeres and Leo J. J. Backx
U.S. Patent No.:		4,267,179
Issued	:	May 12, 1981
For	:	HETEROCYCLIC DERIVATIVES OF (4-PHENYLPIPERAZIN-1-YL-ARYLOXYMETHYL-1,3-DIOXOLAN-2-YL)METHYL-1*H*-IMIDAZOLES AND 1*H*-1,2,4-TRIAZOLES

Hon. Commissioner of Patents and Trademarks
Box Patent EXT
Washington, D.C. 20231

DECLARATION

Dear Sir:

I, Charles J. METZ, residing at 15 Bellegrove Drive, Upper Montclair, New Jersey 07043 , declare as follows:

1) THAT I am a Patent Attorney authorized to practice before the United States Patent and Trademark Office (registration number 20,359) and have general authority to act in patent matters before the United States Patent and Trademark Office on behalf of Janssen Pharmaceutica N.V., the owner of the above-identified patent for which term extension is being requested.

2) THAT I have reviewed and understand the content of the application for patent term extension which is submitted pursuant to 35 U.S.C. §156 of which this Declaration is attached as Exhibit H.

3) THAT I believe that U.S. Patent No. 4,267,179 is subject to extension pursuant to 37 C.F.R. 1.710.

4) THAT I believe an extension of four (4) years, one (1) month and twenty-one (21) days of the term of U.S. Patent No. 4,267,179 is justified under 35 U.S.C. §156 and the applicable regulations.

5) THAT I believe U.S. Patent No. 4,267,179 for which the extension is being sought meets the conditions for extension of the term of a patent as set forth in 37 C.F.R. 1.720.

I hereby declare that all statements made herein of my own knowledge are believed true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so make are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this application and any extension of U.S. Patent No. 4,267,179.

Charles J. Metz

Date: October 29, 1992 Charles J. Metz

STATE OF NEW JERSEY)
)
) ss.
)
COUNTY OF MIDDLESEX)

BE IT REMEMBERED, that on this 29th day of October, 1992, before me, a Notary Public, personally appeared Charles J. Metz, who I am satisfied is the person named in and who executed the foregoing instrument in my presence, and I having first made known to him the contents thereof, he did acknowledge that he signed, sealed, and delivered the same as his voluntary act and deed for the uses and purposes therein expressed.

Joan Weiss

Notary Public
JOAN WEISS
Notary Public of New Jersey
My Commission Expires Sept. 11, 1995

JAB 287

IN THE UNITED STATES
PATENT AND TRADEMARK OFFICE

Inventors : Jan Heeres and Leo J. J. Backx

U.S. Patent No.: 4,267,179

Issued : May 12, 1981

For : HETEROCYCLIC DERIVATIVES OF (4-PHENYLPIPERAZIN-1-YL-ARYLOXYMETHYL-1,3-DIOXOLAN-2-YL)METHYL-1*H*-IMIDAZOLES AND 1*H*-1,2,4-TRIAZOLES

Certificate

"Express Mail" mailing number TB123968746 US

Date of Deposit October 30, 1992

I hereby certify that this complete Application for Extension of Patent Term including the Transmittal Letter and all Exhibits and Attachments named therein is being deposited in duplicate with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to the Commissioner of Patent and Trademarks, BOX PATENT EXT, Washington, D.C. 20231.

Charles J. Metz
(Typed or printed name of person mailing paper or fee)

Charles J. Metz
(Signature of person mailing paper or fee)